PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
12383280/EJH		
International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/001647	9 December 2003	9 December 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] C12N 5/08, A61K 39/395

Applicant

THE CORPORATION OF THE TRUSTEES OF THE ORDER OF THE SISTERS OFMERCY IN QUEENSLAND et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of the report
25 June 2004	6 April 2005
Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**ANITA PREMKUMAR** Telephone No. (02) 6283 2515

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001647

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**18-21, 23-26 and 28**	**YES**
	Claims	**1-17, 22 and 27**	**NO**
Inventive step (IS)	Claims	**none**	**YES**
	Claims	**1-28**	**NO**
Industrial applicability (IA)	Claims	**1-28**	**YES**
	Claims	**none**	**NO**

2. Citations and explanations (Rule 70.7)

The invention lies in a method of generating T-cells specific for an antigen. The method involves co-incubation of mature antigen presenting cells, $CD4^+$ T-cells and $CD8^+$ T-cells for a period of time sufficient to generate a population of $CD8^+$ T-cells specific for the antigen. The antigen presenting cells may be a dendritic cell. The $CD8^+$ T-cells produced could be used in immunotherapy.
A number of prior art documents disclose the use of the method described in the invention for the generation of cytotoxic T-cells.

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: Szmania, S., *et al*; Blood, (2001), 98 (3): 505-512.

D2: Peggs, K., *et al*; Blood, (2002), 99 (1): 213-223.

D3: Re, F., *et al*; Blood, (2002), 100 (11): Abstract No. 2663.

D4: Verfuerth, S., *et al*; Blood, (2000), 96 (11) Part 1: 27a.

D5: Hoffmann, T. K., *et al*; Cancer Research, (2000), 60 (13): 3542-3549

D6: Perez-Diez, A., *et al*; Cancer Research, (1998) 58 (23): 5305-5309

D7: Ito, A., *et al*; Journal of Gastroenterology and Hepatology, (2001) 16 (3): 309-316.

D8: Cho, H. I., *et al*; Journal of Immunotherapy (2001) 24 (3): 242-249.

D9: Peggs, K., *et al*; Blood, (2001), 97 (4) 000: 994-1000.

Supplemental Box V
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of 2

Novelty:
The invention disclosed in claims 1-17, 22 and 27 is not novel when compared with prior art documents D1, D2, D3, D4, D5, D7, D8 and D9.
The invention is a method of generating T-cells specific for an antigen. The method involves co-incubation of mature antigen presenting cells, $CD4^+$ T-cells and $CD8^+$ T-cells for a period of time sufficient to generate a population of $CD8^+$ T-cells specific for the antigen. All the citations disclose a similar method of producing cytotoxic T-cells for use in immunotherapy.

The citations disclose methods of generating cytotoxic T lymphocytes that could be used in immunotherapy. In the citations dendritic cells were pulsed with a peptides or antigens from CMV, MART1 antigen of tumours, EBV. antigens, Aspergillus antigens, apoptotic tumour cells, or HCV peptides. The pulsed dendritic cells were then co-cultured with donor T-cells (containing both CD4+ and CD8+ T-cells) or auotologus peripheral blood lymphocytes (which inherently contain both CD4+ and CD8+ T-cells) to generate CD8+ T-cells specific to a given antigen or peptide. As such the citations disclose all the essential features of claims 1-17, 22 and 27 and therefore the invention is not novel.

Inventive Step:

The invention defined in claims 17-21, 23-26 and 28 does not involve an inventive step in the light of D1, D2, D3, D4, D5, D6, D7, D8 and D9. The invention lies in a method of treating a subject with CD8+ T-cells that have been generated by the method disclosed in the previous claims. Although the citations do not specifically treat subjects with the T-cells generated by the method disclosed, they do provide a sign post for using the cells generated by using proteins as functional adjuvants to generate CD8+ T-cells which can be used to enhance immune response to tumour associated antigens or to infections caused by a pathogen. As such, having read the citations the PSA would be lead to using these peptide/antigen primmed T-cells in the treatment of cancers or infections. Therefore the PSA would directly and without difficulty, by routine steps, arrive at a solution that is the same as the claimed solution, therefore the claims lacks an inventive step.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2003/001647

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C12N 5/08, A61K 39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ABOVE

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE BELOW

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, CAPLUS, BIOSIS, WPIDS (Antigen presenting cells, dendritic cells, CD4, CD8 T-cells, antigen, peptide, macrophages, co-culture

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Szmania, S., *et al*; BLOOD, (2001), 98 (3) : 505-512. Isolation and expansion of cytomegalovirus-specific cytotoxic T lymphocytes to clinical scale from single blood draw using dendritic cells and HLA-tetramers. Abstract; Page 509,col 2, papa 4; Page 509 col 1, para 1.	1-8, 10-28

[X] Further documents are listed in the continuation of Box C [ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2004	20 FEB 2004
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**David Olde** Telephone No : (02) 6283 2569

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2003/001647

C (Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Peggs, K., *et al*; BLOOD, (2002), 99 (1): 213-223. Characterization of human cytomegalovirus peptide-specific $CD8^+$ T-cell repertoire diversity following in vitro restimulation by antigen-pulsed dendritic cells. Abstract; Page 214 lines 23-28; Page 241 Materials and Methods first para; Page 215, col 1 Results first para; Page 218 col 2 Discussion; Page 219, col 2, lines 1-8.	1-28
X	Re, F., *et al*; BLOOD, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 2663. Green Fluorescent Protein (GFP) Expression in Dendritic Cells Enhances Their Immunogenicity and Elicits GFP-Specific Cytotoxic T-Cell (CTL) Responses in Humans. Whole abstract	1-8, 10, 13-15, 17-21, 26-28
X	Verfuerth, S., *et al*; BLOOD, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 27a. A versatile culture system for the in vitro expansion of autologous donor-derived cytomegalovirus, Epstein Barr virus and Aspergillus antigen-specific T cells. Whole abstract	1-8, 10-28
X	Hoffmann, T. K., *et al*; CANCER RESEARCH, (2000 Jul 1) 60 (13) 3542-9 Generation of tumor-specific T-lymphocytes by cross-priming with human dendritic cells ingesting apoptotic tumor cells. Abstract; Introduction; Page 3546 first para.	1-8, 10-12, 15, 17-21, 26-28
X	Perez-Diez, A., *et al*; CANCER RESEARCH, (1998 Dec 1) 58 (23) 5305-9 Generation of CD8+ and CD4+ T-cell response to dendritic cells genetically engineered to express the MART-1/Melan-A gene. Abstract; Page 5305, col 2, lines 32-end; Page 5306 col 1 lines 10-13, 24-26, last para-col 2 lines 1-5.	1-8, 10-21, 26-28
X	Ito, A., *et al*; JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (2001 Mar) 16 (3) 309-16. Generation of hepatitis C virus-specific cytotoxic T lymphocytes from healthy individuals with peptide-pulsed dendritic cells. Abstract; Page 311 last para; Page 313, col 1, lines 31-33.	1-8, 10-15, 17-24, 26-28
X	Cho, H. I., *et al*; Journal of Immunotherapy (2001 May-June) 24 (3): 242-9. Generation of cytotoxic T lymphocytes specific for human cytomegalovirus using dendritic cells in vitro. Abstract; Page 243, col 2, para 1; Page 244, col 2, para 2; Page 246, col 1, lines 14-17.	1-8, 10-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2003/001647

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Peggs, K., *et al*; BLOOD, (2001), 97 (4) : 994-1000. Induction of cytomegalovirus (CMV)-specific T-cell responses using dendritic cells pulsed with CMV antigen: novel culture system free of live CMV virions. Abstract; Page 994 - introduction; Page 995 col 1; Page 995 Materials and Methods; Page 997, col 1 para 1; Table 1; Page 999, col 1, last 2 line - col 2 lines 1-2.	1-8, 10, 11, 13-28